ORIGINAL ARTICLE

sciendo

10.2478/AMB-2024-0002

PERMANENT PACEMAKER IMPLANTATION: EARLY POST-IMPLANTATION DATA

I. Yoncheva[1,2], D. Biserov[1,2], M. Negreva[3]

[1]University Hospital – Burgas, Bulgaria
[2]University Hospital "Virgin Mary" – Burgas, Bulgaria
[3]University Hosptal "Sv. Marina" – Varna, Bulgaria

Abstract. Introduction: *Data on the development of left ventricular dysfunction after permanent pacemaker implantation are available. Myocardial collagen deposition is a well-known mechanism that occurs in left ventricular remodelling. This gave us reason to dynamically monitor the levels of the main molecules involved in collagen synthesis, PIPC (carboxy-terminal propeptide of type I procollagen) and PIIINP (amino-terminal propeptide of type III procollagen).* ***Materials and Methods:*** *PIPC and PIIINP levels were studied using enzyme-linked immunoassays in plasma from 45 patients (25 men, 20 women, 72.1 ± 9 years) and 46 controls (24 men, 22 women, 71.9 ± 8.7 years) without known cardiovascular diseases (except arterial hypertension, conduction disorder, indication for the procedure) at baseline (immediately before PPM implantation for patients), at 12 and 24 weeks.* ***Results:*** *There was no difference in baseline levels of PICP and PIIINP between patients and controls (p > 0.05, Table abstract). At week 12, PICP levels increased significantly in patients compared to baseline in controls (p < 0.05, Table abstract). At week 24, values continued to increase and were again significantly higher than baseline in the controls (p < 0.001, Table abstract). At the 12-week follow-up visit, PIIINP values in patients were significantly higher than those at baseline in controls (p < 0.001, Table abstract). At week 24, the values of the patients were still higher than those of the controls, but the difference was not significant (p > 0.05, Table abstract).* ***Conclusion:*** *This study showed early activation of collagen synthesis < 6 months after PPM (permanent pacemaker) implantation. Due to the selection of patients without concomitant cardiovascular pathology, we have reason to assume that it is a result of the procedure itself and a serious prerequisite for increased collagen deposition in the myocardium.*

Key words: *PIPC, PIIINP, permanent pacemaker*

Corresponding author: *Ivaneta Dimitrova Yoncheva, 73 Stefan Stambolov bul., 8000 Burgas, Bulgaria. Phone number: +359887260307, e-mail: Ivaneta.yoncheva@gmail.com, OrcID: 0000-0002-0965-1833*

Received: *09 June 2023;* ***Revised/Accepted:*** *17 July 2023*

INTRODUCTION

Since the introduction of PPM implantation as part of the therapeutic approach in patients with bradyarrhythmias, data on its undisputed benefits have rapidly accumulated [1, 2, 3]. Over the years, dual chamber pacing has become a standard approach for the treatment of permanent or paroxysmal third- or high-degree atrioventricular block (AVB) [4, 5]. Life expectancy of heart disease patients has also increased significantly with improved primary and secondary prevention [6, 7]. This led to an in-

crease in the number of PPM implantations and allowed us to analyze its long-term effects. In addition to the indisputable benefits of dual chamber pacing, there are convincing data on the negative influence of apical right ventricular stimulation on heart pump parameters [8, 9, 10]. Reduction in left ventricular (LV) stroke volume, inefficient LV emptying, and appearance of functional mitral regurgitation were observed. Their manifestation is associated with asynchronous apical right ventricular (RV) stimulation [11]. At the end of the tenth year, development of heart failure (HF) was observed in approximately 20% of patients with an implanted dual chamber pacemaker [12, 13]. According to some authors, changes in LV function occurred as early as the end of the first year, when a decrease in ejection fraction (EF) of more than 10% was recorded [14].

These results predetermine the need to look for opportunities to overcome the established limitations of apical RV pacing, one of which is the development of alternative pacing methods, that approximate as closely as possible the physiological pathway of myocardial depolarisation in areas close to the heart conduction system (His bundle (HB), left bandle area (LBA), etc.), as well as multipoint pacing [15, 16, 17, 18, 19, 20, 21]. The pathophysiological mechanisms involved in myocardial remodelling during pacemaker stimulation and how to overcome their influence have been increasingly discussed [22]. Some authors emphasise that the process is individual and probably multifactorial [23]. A common principle in the development of myocardial contractile disorders is the remodelling of the extracellular matrix at the expense of increased interstitial replacement fibrosis [24]. There is activation of myofibroblasts and increased collagen production in the interstitium, which is an expression of contractile dysfunction [25, 26]. The intimate mechanisms of this process, as well as the timing of their development, remain unspecified [27, 28, 29, 30].

The data presented above gave us reason to conduct the present study, the objective of which was to investigate the fibrotic response in patients after PPM implantation with apical RV stimulation by dynamically examining the main molecules of collagen synthesis: PIPC and PIIINP.

MATERIALS AND METHODS

Study design

The study was conducted in the Cardiology Department at the Virgin Mary University Hospital, Burgas, Bulgaria for the period March 2019 – August 2021. Inclusion of patients and controls began after approval of the Research Ethics Committee at the Medical University of Varna, No 82, March 28th, 2019 and the Virgin Mary University Hospital, Burgas, No. 502, March 21st, 2019, in compliance with the requirements of the Declaration of Helsinki (The World Medical Association, Declaration of Helsinki, 2008). Participants over 18 years of age were included after prior explanation and signing of an informed consent to participate.

Two groups were formed, patients and controls. Selection of study participants was based on clearly formulated inclusion and exclusion criteria (see below).

The study was designed to equalise the demographic and clinical characteristics of both groups in order to minimise the possibility of selection bias and compare them objectively [31]. This contributed to the reliability of the conclusions, as well as the established cause-and-effect relationships. The control group was created similar to the patient group in terms of gender, age, and comorbidities.

For the purpose of the study, peripheral venous blood was drawn from a cubital vein, and the levels of PICP and PIIINP were examined in each participant. Transthoracic echocardiography was performed on the day after PPM implantation to avoid the effect of atrioventricular asynchrony on LV pump parameters.

Collagen synthesis parameters were determined thrice in patients: immediately before PPM implantation (baseline value or visit 1 – V1), at 12 weeks (visit 2 – V2) and 24 weeks (visit 3 – V3) after implantation. The same parameters were also examined thrice in controls: at baseline (visit 1 – V1), at 12 weeks (visit 2 – V2) and 24 weeks (visit 3 – V3) after selection for the study. Blood was centrifuged, and the resulting plasma was frozen and stored according to the requirements of the assays used. The control group underwent ECG and echocardiography examination after their inclusion in the study. At follow-up visits, blood was drawn to examine fibrosis indices, and participants were also questioned about new complaints and diseases.

Indication for implantation in the patients included in the study was presence of complete AVB. After signing informed consent, they were implanted with a dual chamber pacemaker (PPM in DDDR mode) according to the requirements described in the EHRA (European Heart Rhythm Association) expert consensus for this type of procedure [5]. This ensured sustained apical RV pacing above 80% in all participants, which was verified by telemetry at each follow-up visit. For the purposes of the study all participants underwent transthoracic echocardiography on the day after implantation to assess LV pump parameters and rule out structural heart disease.

Study population

For the purpose of the study, 144 patients were screened from whom 45 patients (25 men, 20 women, 72.18 ± 1.35 years) without known cardiovascular disease (except arterial hypertension and conduction disorder, indication for the procedure) were selected. 99 were excluded from the study due to exclusion criteria (see below).

The control group was formed after screening 102 patients, and 46 (24 men, 22 women, 71.96 ± 1.29 years) were selected according to the set inclusion and exclusion criteria and included in the study after signing informed consent. The controls had no history and ECG evidence of current rhythm-conduction pathology. 39 of them had arterial hypertension as a comorbidity, which was optimally controlled with medications.

For the purposes of the study, it was of utmost importance to minimise the impact of medications and comorbidities on fibrotic response in selected patients and controls. For this reason, both patients and controls were treated with pharmaceuticals for which there is currently no evidence of a direct effect on the renin-angiotensin aldosterone system (RAAS). After selection, participants were treated with one or a combination of the following medications: a dihydropyridine calcium antagonist (amlodipine), thiazide diuretic (hydrochlorothiazide), and, if necessary, a centrally acting medication (methyldopa), in doses needed to achieve blood pressure control.

Inclusion criteria for the patient group

1. Presence of complete AVB as an indication for implantation of a dual chamber pacemaker.
2. Eligible comorbidity: moderate arterial hypertension that was medically well-controlled.
3. Absence of exclusion criteria.

Inclusion criteria for the control group

1. No history or ECG evidence of rhythm-conduction pathology.
2. Eligible comorbidity: moderate arterial hypertension that was medically well-controlled.
3. Absence of exclusion criteria.

Exclusion criteria:

1. Presence of cardiovascular disease: coronary artery disease (acute coronary syndrome; history of myocardial infarction, regardless of age; coronary revascularisation PCI/CABG; stable angina pectoris); heart failure with depressed pump function; uncontrolled hypertension; inflammatory heart disease: myocarditis, pericarditis, infective endocarditis; congenital heart disease; clinically significant acquired valvular heart disease; cardiomyopathies; thromboembolic events.
2. Presence of other diseases: renal or liver failure; diseases of the central nervous system; inflammatory and/or infectious diseases in the last three months; neoplastic or autoimmune diseases; nutritional pulmonary disease; diseases of the endocrine system; surgical intervention in the last three months;
3. Presence of pregnancy, systemic intake of NSAIDs (non-steroidal anti-inflammatory drugs) and antithrombotic drugs and mineralocorticoid antagonists.

Collection and storage of blood samples

Blood samples were obtained after puncture of the cubital vein (left or right) with a vacutainer system. Venous blood samples were centrifuged for 15 min at 3500 rpm. The separated serum was frozen at -20 C and after 3 to 4 weeks transferred for storage at -80 C. Included patients had 3 blood samples taken as follows: at baseline before pacemaker implantation, at 12 and at 24 weeks after implantation. Patients in the control group had identical amounts of blood samples taken, processed, and tested according to the same protocol.

Laboratory procedures

Factors tested: PICP and PIIINP were quantified by the ELISA method with MyBioSource kits from Human PICP Sandwich – ELISA and Human PIIINP Sandwich – ELISA (MyBioSource, Inc. San Diego, USA) as follows:

1. Human carboxy-terminal propeptide of type I procollagen, PICP ELISA Kit with a sensitivity of 2.26 ng/ml
2. Human aminoterminal propeptide of type III procollagen, PIIINP ELISA Kit with a sensitivity of 1.0 ng/ml.

Statistical analysis

All analyses were performed with STATISTICA 13.3.0, StatSoft Inc, USA.

Continuous variables were expressed as mean ± Standard Error of the Mean (SEM) and categorical variables were expressed as percentage of the total group. Two-tailed Student's t-test for independent samples was used to compare quantitative variables measured in controls and patients. Values $p < 0.05$ were adopted for statistically significant.

RESULTS

There were no statistical differences between patients and controls in terms of number, mean age, sex, and BMI ($p > 0.05$) as seen in Table 1.

Table 1. Demographic characteristics of patient and control groups

	Patients	Controls	P value
Number of participants	45	46	> 0.05
Mean age	72.18 ± 1.35	71.96 ± 1.29	> 0.05
Men/Women	25/20	24/22	> 0.05
BMI (kg/m^2)	27.45 ± 0.64	26.51 ± 0.49	> 0.05

According to the study design, the patient and control groups had no significant differences in comorbidities ($p > 0.05$) and antihypertensive therapy ($p > 0.05$) as seen in Table 2.

Table 2. Clinical characteristics of patient and control groups

	Patients (%)	Controls (%)	P value
Comorbidities			
Hypertensive disease	39 (86.66 %)	37 (80.43%)	> 0.05
Antihypertensive therapy			
Dopegit	23 (51.11%)	24 (52.17%)	> 0.05
Amlodipine	35 (77.78%)	33 (71.74%)	> 0.05
Hydrochlorothiazide	35 (77.78%)	35 (76.09%)	> 0.05

Transthoracic echocardiography did not reveal significant differences between LV end-diastolic and end-systolic volume, as well as in ejection fraction in the patient and control groups. Additionally, the measured values were within the normal range accepted by the European Association of Cardiovascular Imaging [32].

Table 3. Transthoracic echocardiography data

Echocardiographic indicator	Patients	Controls	P value
LVEDV	51.98 ± 1.97	52.17 ± 1.65	> 0.05
LVESV	24.50 ± 0.77	24.52 ± 0.76	> 0.05
EF%	57.36 ± 0.66	55.98 ± 0.33	> 0.05

2.2.1 PICP deviations

It is clear from Figure 1 that baseline values in patients were not different from those of controls (85.13 ± 4.68 vs 79.34 ± 3.49 ng/ml, $p > 0.05$). At week 12 (patients V2), PICP levels had increased significantly compared to controls (90.51 ± 4.28 vs 79.34 ± 3.49 ng/ml, $p = 0.0445$), and at week 24 (patients V3) the increasing trend was sustained (161.35 ± 14.05 vs 79.34 ± 3.49 ng/ml, $p < 0.001$).

Comparison of values in the patient group (Figure 2) showed that at week 12 (patients V2) PICP levels

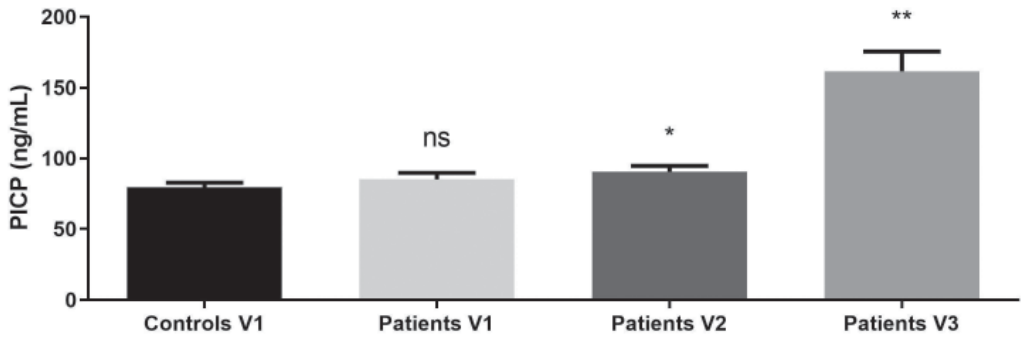

Fig. 1. Comparison of PICP values at baseline (patients V1), week 12 (patients V2) and week 24 (patients – V3) versus baseline in the control group (controls V1). (* $p < 0.05$; ** $p < 0.001$; ns- statistically insignificant difference)

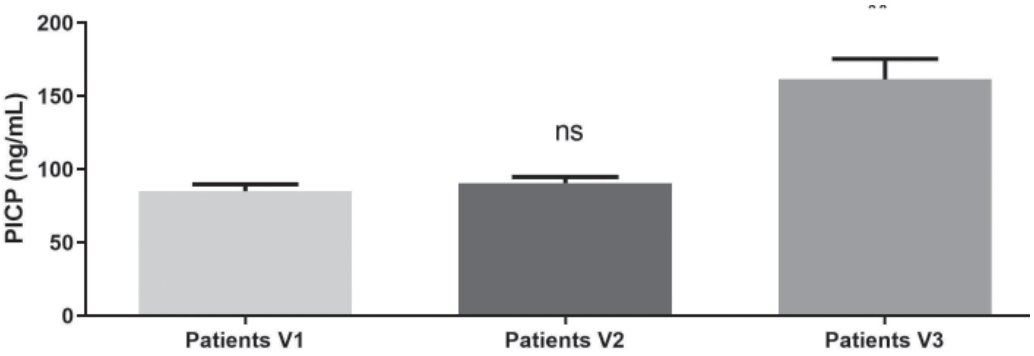

Fig. 2. Dynamics of PICP levels in the patient group: baseline (patients V1), at week 12 (patients V2) and at week 24 (patients V3). (* $p < 0.05$; ** $p < 0.001$; ns- statistically insignificant difference)

had increased from baseline (patients V1) (90.51 ± 4.28 vs 85.13 ± 4.68 ng/ml, p < 0.05), but this increase was not significant. At week 24 (patients V3), absolute values continued to increase and were now significantly higher compared to baseline levels (patients V1) (161.35 ± 14.05 vs 85.13 ± 4.68 ng/ml, p < 0.001).

There were no significant changes in plasma levels of the indicator during follow-up in the control group. There was also no significant difference between the values at the second and third visits compared to baseline (80.91 ± 4.14 vs 79.34 ± 3.49 ng/ml; 85.26 ± 4.75 vs 79.34 ± 3.49 ng/ml, p > 0.05). There were no significant differences in levels between the third and second visit follow-ups (85.26 ± 4.75 vs 80.91 ± 4.14 ng/ml, p > 0.05) (see Figure 3).

2.2.2 PIIINP deviations

Figure 4 shows that baseline values in patients did not differ from controls (4.11 ± 0.20 vs 3.94 ± 0.24 ng/ml, p > 0.05). At week 12, levels in patients (patients V2) had increased significantly compared to baseline levels of controls (6.95 ± 0.56 vs 3.94 ± 0.24 ng/ml, p < 0.001). At week 24, patient values (patients V3) had fallen to levels that were higher than controls, but the difference was not significant (4.56 ± 0.20 vs 3.94 ± 0.24 ng/ml, p > 0.05).

PIIINP levels in the patient group at week 12 (Figure 5) (patients V2) had increased significantly from baseline (patients V1) (6.95 ± 0.56 vs 4.11 ± 0.20 ng/ml, p < 0.001). At week 24 (patients V3), PIIINP levels had decreased, still higher than baseline, although the difference was not statistically significant (4.56 ± 0.20 vs 4.11 ± 0.20 ng/ml p > 0.05)

There were no significant changes in the plasma levels of the indicator during the follow-up period in the control group – no significant differences were found between the values of the second and third visits compared to baseline (4.60 ± 0.32 vs 3.94 ± 0.24 ng/

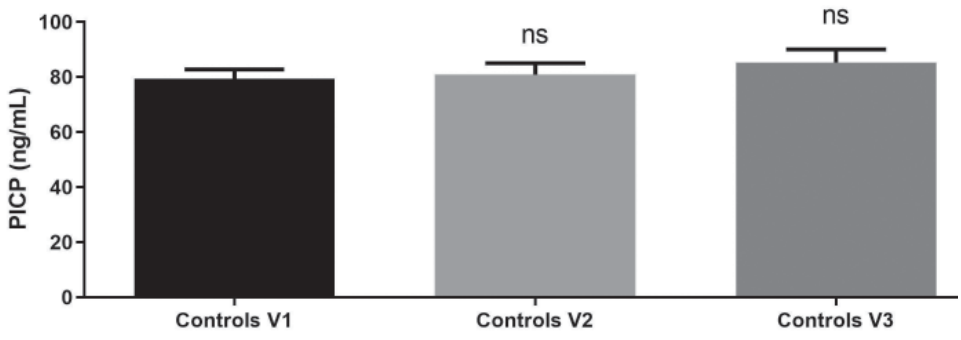

Fig. 3. Dynamics in PICP levels in the control group: baseline (controls V1), at week 12 (controls V2) and at week 24 (controls V3); ns- statistically insignificant difference

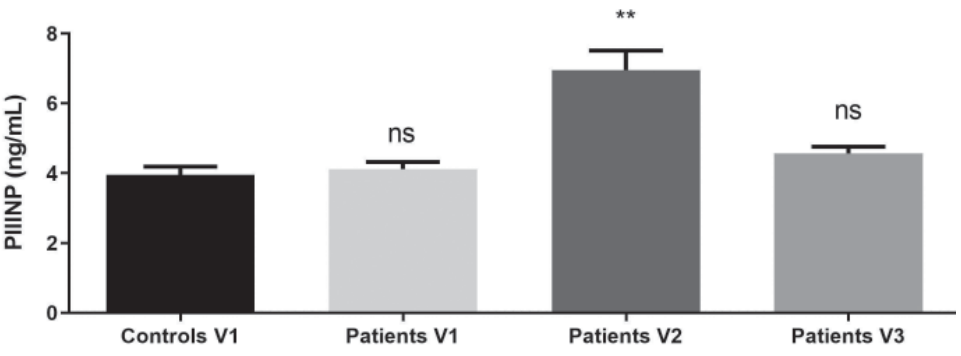

Fig. 4. Comparison of PIIINP values at baseline (patients V1), at week 12 (patients V2) and week 24 (patients V3) with baselines in the control group (controls V1). (*p < 0.05; **p < 0.001; ns – statistically insignificant difference)

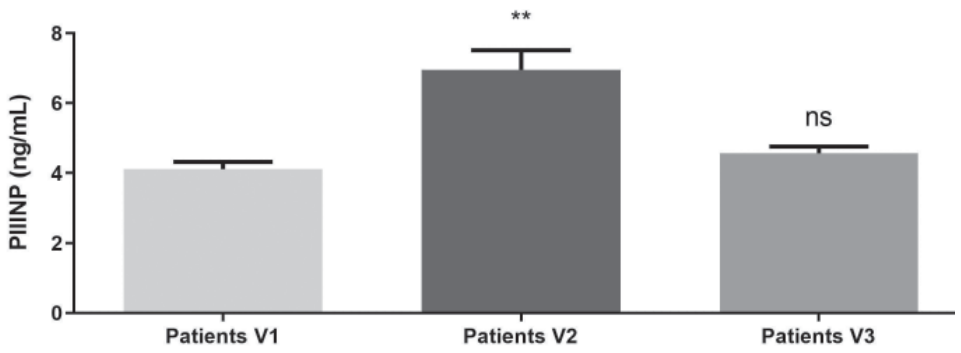

Fig. 5. Dynamics of PIIINP levels in the patient group: baseline (patients V1), at week 12 (patients V2) and at week 24 (patients V3). (*p < 0.05; **p < 0.001; ns – statistically insignificant difference)

ml; 4.06 ± 0.29 vs 3.94 ± 0.24 ng/ml, p > 0.05). There were no significant differences in follow-up levels at the third and second visit (4.06 ± 0.29 vs 4.60 ± 0.32 ng/ml, p > 0.05) (Figure 6).

DISCUSSION

In 1994, experimental models showed that constant RV apical pacing for 14 weeks resulted in regional changes in myocardial perfusion, increased catecholamine activity, and development of diastolic dysfunction [33]. There is now strong evidence of negative consequences on cardiac function as a result of pacing-induced asynchronous LV contraction [34]. ECM remodelling underlies the development of systolic and diastolic dysfunction over time in PPM patients [35, 36]. Data from studies have shown that after 12 weeks of constant RV stimulation, heterogeneous changes in ECM, increased MMP-2 and MMP-9 activity and increases in collagen type I mRNA levels were observed [37]. According to the implemented study design, our team aimed to look for early changes in collagen synthesis biomarkers after PPM implantation. The results showed that PICP levels increased at week 12 after implantation compared to controls, although with a cutoff value of p = 0.0445 (Figure 1). At week 24, there was a significant increase in PICP, both relative to baseline values in patients (p < 0.001) (Figure 2) and baseline values in controls (p < 0.001) (Figure 1). This gave us reason to assume that PPM implantation leads to an extremely early activation of collagen metabolism. The ECM in the myocardium has been shown to have a specific composition and contains mainly type I (85%) and type III collagen (11%) [38]. Current understanding is that the cardiac interstitium is a dynamic reticular structure with important metabolic activity [39]. Under the influence of a pathological stimulus, fibroblast activation occurs, leading to increased collagen synthesis [25,40]. Patients with advanced heart failure have an increased collagen content in the interstitium, leading to deeper pathophysiological consequences and disease progression [38,41]. In recent years, PICP and PIIINP levels have established themselves as reliable molecules for assessing collagen metabolism [42,43]. Data from previous studies suggest that both the amount of interstitial collagen and type I/III collagen ratio are important for development of cardiac dysfunction [44]. An increase in this ratio is associated with reduced LV wall elasticity and cavity dilatation. In the patient group, there was an increase in PIIINP levels at week 12, both relative to baseline in patients (p < 0.001) (Figure 5) and baseline in controls (p < 0.001) (Figure 4). However, at week 24 after implantation, there was a decrease to similar, but higher, levels than at baseline. Although there was a trend to increase toward the end of the follow-up period, the difference was not significant. Regarding the significant increase at week 12 after implantation, we can suggest that it might probably be a result of the surgical intervention. It is an undeniable fact that collagen type III is involved in the construction of the skin and subcutaneous tissue and plays an active role in the healing of the surgical cicatrix [45]. A study of samples taken from surgical wounds found a significant increase in PIIINP levels in the days following

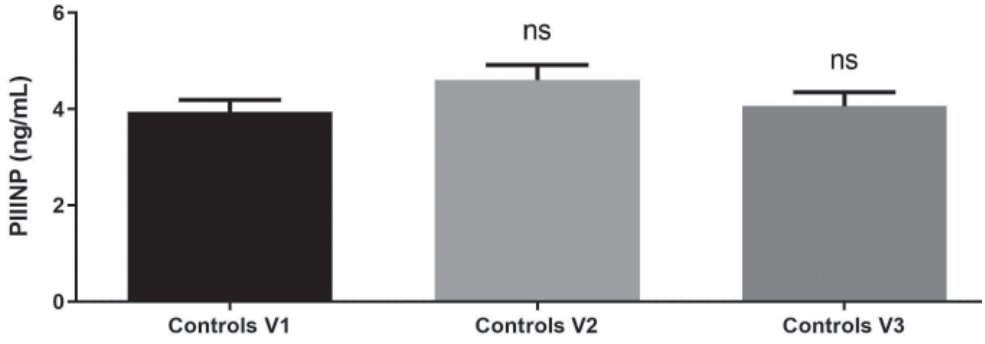

Fig. 6. PIIINP dynamics in the control group: baseline, at inclusion in the study (V1 controls V1), at week 12 (V2 controls) and at week 24 (V3 controls); ns- statistically insignificant difference

Table 4. Plasma PICP and PIIINP concentrations in patients after dual-chamber PPM implantation and controls

	PICP/V1 ng/ml	PICP/V2 ng/ml	PICP/V3 ng/ml	PIIINP/V1 ng/ml	PIIINP/V2 ng/ml	PIIINP/V3 ng/ml
Patients	85.13 ± 4.68	90.51 ± 4.28	161.35 ± 14.05	4.11 ± 0.20	6.95 ± 0.56	4.56 ± 0.20
Controls	79.34 ± 3.49	80.91 ± 4.14	85.26 ± 4.75	3.94 ± 0.24	4.60 ± 0.32	4.06 ± 0.29

V1 – Visit 1, baseline; V2 – Visit 2, 12 weeks after V1; V3 – Visit 3, 24 weeks after V1

intervention [46]. Serum levels of this marker have also been found to rise several times above those of nonoperated patients, and then gradually decline to baseline values. Despite the lack of significant differences between the two groups, there was a trend toward higher values in patients, as indicated by the cutoff value of p = 0.15. Whether the increasing trend will be maintained can be ascertained by monitoring the levels of this indicator over a longer period.

Collagen deposition in reactive myocardial fibrosis increases myocardial stiffness, leading to expression of systolic and diastolic dysfunction [47, 48, 49]. This is due to a greater amount of type I collagen, which has large-diameter fibers and is highly cross-linked compared to type III [43]. In patients with congestive heart failure, there is a positive correlation between PICP levels and LV size, deterioration of LV systolic function, BNP levels, and appearance of intraventricular asynchrony [50]. However, these results were determined only once in patients with clinical signs of congestive heart failure already demonstrated. Similar results have been found in patients with an implantable cardioverter-defibrillator (ICD) [51]. Data show that patients with registered tachycardia, requiring device therapy, had lower LV ejection fraction and higher PICP/PIIINP ratio. In this study, serum markers of collagen synthesis were also examined once before defibrillator implantation, and the change in values over time was unknown.

According to our study design, all patients had preserved LV systolic function at baseline, determined by echocardiography on the day after pacemaker implantation. As has been shown, changes in the myocardial interstitium can occur in various pathological conditions [52, 53]. Therefore, the included patients were free of serious comorbidities that might have affected fibrotic activity during follow-up. On the other hand, with natural processes that occur in the biological ageing of the body, there is an increase in collagen deposition in different tissues and organs [25]. This was the reason for tracing collagen synthesis markers in parallel and dynamically in both the patient and control groups. Based on the above, we can assume that the increase in PICP and PIIINP levels at week 24 was due to PPM-induced asynchronous ventricular contraction.

CONCLUSION

Our study showed early activation of collagen synthesis as early as 6 months after PPM implantation. Due to the selection of patients without concomitant cardiovascular disease, we have reason to assume that these changes were probably the result of asynchronous LV contraction. From the data we obtained in the dynamic follow-up of collagen synthesis markers, the development of a profibrotic state was evident, which we can assume to be an expression of ECM remodelling.

Disclosure Summary: *The authors have nothing to disclose.*

REFERENCES

1. Breur JM, Udink Ten Cate FE et al. Pacemaker therapy in isolated congenital complete atrioventricular block. Pacing. Clin Electrophysiol. 2002; 25:1685-1691.
2. Vanagt WY, Verbeek XA, Delhaas T et al. The left ventricular apex is the optimal site for pediatric pacing: correlation with animal experience. Pacing Clin Electrophysiol. 2004, 27:837-843.
3. Healey JS, Toff WD, Lamas GA, et al. Cardiovascular outcomes with atrial-based pacing compared with ventricular pacing: meta-analysis of randomized trials, using individual patient data. Circulation. 2006, 114:11-17.
4. Boriani G, Tukkie R, Manolis AS et al. MINERVA Investigators. Atrial antitachycardia pacing and managed ventricular pacing in bradycardia patients with paroxysmal or persistent atrial tachyarrhythmias: the MINERVA randomized multicentre international trial. Eur Heart J. 2014, 35:2352-2362.
5. Burri H, Starck C, Auricchio A et al. EHRA expert consensus statement and practical guide on optimal implantation technique for conventional pacemakers and implantable cardioverter-defibrillators: endorsed by the Heart Rhythm Society (HRS), the Asia Pacific Heart Rhythm Society (APHRS), and the Latin-American Heart Rhythm Society (LAHRS). Europace. 2021, doi: 10.1093/europace/euaa367.
6. Phyo AZZ, Freak-Poli R, Craig H et al. Quality of life and mortality in the general population: a systematic review and meta-analysis. BMC Public Health. 2020, 20(1):1596.
7. Martinez R, Morsch P, Soliz P, et al. Life expectancy, healthy life expectancy, and burden of disease in older people in the Americas, 1990- 2019: a population-based study. Rev Panam Salud Publica. 2021; 30(9):45-114.
8. Li C, Li C, Bai W, et al. Value of three- dimensional speckle-tracking in detecting left ventricular dysfunction in patients with aortic valvular diseases. J Am Soc Echocardiogr. 2013; 26:1245-52.
9. Xu H, Li J, Bao Z, et al. Early Change in Global Longitudinal Strain is an Independent Predictor of Left Ventricular Adverse Remodelling in Patients with Ventricular Apical Pacing. Heart, Lung and Circulation. 2019; 28(12):1780-1787. https://doi.org/10.1016/j.hlc.2018.11.004
10. Cevher V, Karaaslan M, Akilli R, et al. Evaluation of the relationship between dyssynchrony and myocardial fibrosis markers in patients with cardiac resynchronization therapy. Ann Med Res. 2020; 27(4):1234-40. doi.org/10.1016/j.amjcard.2018.03.159
11. Strauss D, Selvester R, Wagner G. Defining left bundle branch block in the era of cardiac resynchronization therapy. Am J Cardiol. 2011; 107:927-934. https://doi.org/10.1016/j.amjcard.2010.11.010
12. Khurshid S, Epstein AE, Verdino RJ, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy. Heart Rhythm. 2014; 11:1619-1625. http://dx.doi.org/10.1016/j.hrthm.2014.05.040

13. Kiehl EL, Makki T, Kumar R, et al. Incidence and predictors of right ventricular pacing-induced cardiomyopathy in patients with complete atrioventricular block and preserved left ventricular systolic function. Heart Rhythm. 2016; 13:2272-2278.
14. Bansal R, Parakh N, Gupta A et al. Incidence and predictors of pacemaker-induced cardiomyopathy with comparison between apical and non-apical right ventricular pacing sites. J Interv Card Electrophysiol. 2019, 56:63-70. doi.org/10.1007/s10840-019-00602-2
15. Hussain M, Furuya-Kanamori L, Kaye G, et al. The Effect of Right Ventricular Apical and Nonapical Pacing on the Short- and Long-Term Changes in Left Ventricular Ejection Fraction: A Systematic Review and Meta-Analysis of Randomized-Controlled Trials. Pacing and Clinical Electrophysiology. 2015; 38(9):1121-1136. doi:10.1111/pace.1268110.1111/pace.12681
16. Cano O, Andres A, Alonso P, et al. Incidence and predictors of clinically relevant cardiac perforation associated with systematic implantation of active-fixation pacing and defibrillation leads: a single-centre experience with over 3800 implanted leads. Europace. 2017; 19:96-102.
17. Zanon F, Ellenbogen K, Dandamudi G et al. Permanent His-bundle pacing: a systematic literature review and meta-analysis. Europace. 2018; 20:1819-1826. https://doi.org/10.1093/europace/euy058.
18. Leong DP, Mitchell AM, Salna I et al. Long-term mechanical consequences of permanent right ventricular pacing: Effect of pacing site. J Cardiovasc Electrophysiol. 2010; 21:1120-1126.
19. Lewicka-Nowak E, Dabrowska-Kugacka A, Tybura S et al. Right ventricular apex versus right ventricular outflow tract pacing: Prospective, randomised, long-term clinical and echocardiographic evaluation. Kardiol Pol. 2006; 64:1082-1091.
20. Flevari P, Theodorakis G, Leftheriotis D. Serum markers of deranged myocardial collagen turnover: Their relation to malignant ventricular arrhythmias in cardioverter-defibrillator recipients with heart failure. Am. Heart J. 2012; 164:530-537. https://doi.org/10.1016/j.ahj.2012.07.006
21. Cano O, Osca J, Sancho-Tello MJ et al. Comparison of effectiveness of right ventricular septal pacing versus right ventricular apical pacing. Am J Cardiol. 2010; 105:1426–1432.
22. Ferrario C. Cardiac remodelling and RAS inhibition. Therapeutic Advances in Cardiovascular Disease. 2016; 10(3):162-171. doi: 10.1177/1753944716642677
23. Ahmed M, Gorcsan 3rd J, Marek J, et al. Right ventricular apical pacing-induced left ventricular dyssynchrony is associated with a subsequent decline in ejection fraction. Heart Rhythm. 2014; 11:602-8.
24. Kai H, Mori T, Tokuda K, et al. Pressure overload-induced transient oxidative stress mediates perivascular inflammation and cardiac fibrosis through angiotensin II. Hypertens Res. 2006; 29:711-718.
25. Jong S, Veen T, Rijen H, et al. Fibrosis and cardiac arrhythmias. J Cardiovasc Pharmacol, 2011; 57:630-638. doi: 10.1097/FJC.0b013e318207a35f
26. Creemers EE, Pinto YM. Molecular mechanisms that control interstitial fibrosis in the pressure-overloaded heart. Cardiovasc Res. 2011; 89:265-272. doi:10.1093/cvr/cvq308
27. Suthahar N, Meijers WC, Silljé HHW, et al. From inflammation to fibrosis-molecular and cellular mechanisms of myocardial tissue remodelling and perspectives on differential treatment opportunities. Curr Heart Fail Rep. 2017; 14:235-250.
28. Besler C, Lang D, Urban D et al. Plasma and cardiac galectin-3 in patients with heart failure reflects both inflammation and fibrosis: implications for its use as a biomarker. Circ Heart Fail. 2017;10(3). DOI:10.1161/CIRCHEARTFAILURE.116.003804
29. Schirone L, Forte M, Palmerio S, et al. A review of the molecular mechanisms underlying the development and progression of cardiac remodeling. Oxid Med Cell Longev. 2017; (3920195):1-16.
30. Ziegler KA, Ahles A, Wille T, et al. Local sympathetic denervation attenuates myocardial inflammation and improves cardiac function after myocardial infarction in mice. Cardiovasc Res. 2018; 114:291-299.
31. Kang M, Ragan BG, Park JH. Issues in outcomes research: an overview of randomization techniques for clinical trials. J Athl Train. 2008; 43(2):215-221
32. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an up- date from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015; 16(3):233-270
33. Lee M, Dae M, Langberg J, et al. Effects of long-term right ventricular apica pacing on left ventricular perfusion, innervation, function and histology. Journal of the American College of Cardiology. 1994; 24(1):225-232. https://doi.org/10.1016/0735-1097(94)90567-3
34. Ravassa S, Ballesteros G, Lopez B, et al. Combination of circulating type I collagen-related biomarkers is associated with atrial fibrillation. J. Am. Coll. Cardiol. 2019; 73: 1398-141.
35. Ducharme A, Frantz S, Aikawa M, et al. Targeted deletion of matrix metalloproteinase-9 attenuates left ventricular enlargement and collagen accumulation after experimental myocardial infarction. J Clin Invest. 2000; 106:55-62.
36. Spinale FG: Matrix metalloproteinases: Regulation and dysregulation in the failing heart. Circ Res. 2002; 90:520-530.
37. Lin L, Lai L, Lin C et al. Left Ventricular Extracellular Matrix Remodeling in Dogs with Right Ventricular Apical Pacing. J Cardiovasc Electrophysiol, 2010; 21(10):1142-1149. doi:10.1111/j.1540-8167.2010.01765.x
38. Kong P, Christia P, Frangogiannis N. The pathogenesis of cardiac fibrosis. Cell Mol. Life Sci. 2014; 71:549-574. https://doi.org/10.1007/s00018-013-1349-6
39. Jarvelainen H, Sainio A, Koulu M, et al. Extracellular matrix molecules: Potential targets in pharmacotherapy. Pharmacol. Rev. 2009; 61:198-223. doi.org/10.1124/pr.109.001289
40. Espeland T, Lunde I, Amundsen B, et al. Myocardial fibrosis. Tidsskriftet. 2018; 138. doi: 10.4045/tidsskr.17.1027
41. Segura A, Frazier O, and Buja L. Fibrosis and heart failure. Heart Fail. Rev. 2014; 19:173-185. doi: 10.1007/s10741-012-9365-4
42. Prockop D and Kivirikko K. Collagens: molecular biology, diseases, and potentials for therapy. Annu. Rev. Biochem. 1995; 64:403-434. doi: 10.1146/annurev.bi.64.070195.002155
43. Lopez B, Gonzalez A, Ravassa S et al. Circulating biomarkers of myocardial fibrosis: the need for a reappraisal. J. Am. Coll. Cardiol. 2015; 65:2449-2456. doi: 10.1016/j.jacc.2015.04.026
44. Uchinaka A, Yoshida M, Tanaka K, et al. Overexpression of collagen type III in injured myocardium prevents cardiac systolic dysfunction by changing the balance of collagen distribution. The Journal of Thoracic and Cardiovascular Surgery. 2018; 156(1):217-226. https://doi.org/10.1016/j.jtcvs.2018.01.097
45. Riekki R, Harvima, JI, Ristile J, Oikarinen A. The production of collagen and the activity of mast-cell chymase increase in human skin after irradiation therapy. Experimental Derma-

tology. 2004; 13(6):364-371. https://doi.org/10.1111/j.0906-6705.2004.00164.x
46. Haukipuro K, Risteli L, Kairaluoma M, et al. Aminoterminal propeptide of type III procollagen in healing wound in humans. Ann Surg 1987; 206:752-756. doi: 10.1097/00000658-198712000-00011
47. Zile M, Desantis S, Baicu C et al. Plasma biomarkers that reflect determinants of matrix composition identify the presence of left ventricular hypertrophy and diastolic heart failure. Circ Heart Fail 2011; 4:246-256. https://doi.org/10.1161/CIRCHEARTFAILURE.110.958199
48. Michalski B, Trzcinski P, Kupczynska K et al, The differences in the relationship between diastolic dysfunction, selected biomarkers and collagen turn-over in heart failure patients with preserved and reduced ejection fraction. Cardiol J. 2017; 24:35-42. DOI: 10.5603/CJ.a2016.0098
49. Duprez D, Gross M, Kizer J, et al. Predictive value of collagen biomarkers for heart failure with and without preserved ejection fraction: MESA (Multi – Ethnic Study of Atherosclerosis). J Am Heart Assoc. 2018; 7:e007885. https://doi.org/10.1161/JAHA.117.007885
50. Löfsjögård J, Thomas K, Javier D et al. Biomarkers of collagen type I metabolism are related to B-type natriuretic peptide, left ventricular size, and diastolic function in heart failure. J Cardiovasc Med, 2014; 15(6):463-469; doi: 10.2459/01.JCM.0000435617.86180.0
51. Flevari P, Leftheriotis D, Fountoulaki K, et al. Long-term non-outflow septal versus apical right ventricular pacing: Relation to left ventricular dyssynchrony. Pacing Clin Electrophysiol. 2009; 32:354-362.
52. Velagaleti R, Vasan R. Heart failure in the twenty-first century: is it a coronary artery disease or hypertension problem? Cardiol Clin. 2007; 25:487-495. doi.org/10.1016/j.ccl.2007.08.010
53. McMurray J, Adamopoulos S, Anker S et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2012; 33:1787-1847. DOI: 10.1093/eurheartj/ehs104